COROSOLIC ACID FORMULATION AND ITS APPLICATION FOR WEIGHT-LOSS MANAGEMENT AND BLOOD SUGAR BALANCE

FIELD OF THE INVENTION

This invention relates to an improved food supplement formulation including corosolic acid for producing sustained weight-loss management and blood sugar balance effects. This food supplement may also improve high blood sugar levels in subjects suffering from type 2 diabetes or non-insulin dependent diabetes mellitus (NIDDM).

BACKGROUND OF THE INVENTION

The first diagnosis of diabetes dates back to Greece, 2,000 years ago. Blood sugar balance, in general, diabetes, in particular, ever since has been the subject of an increasing scientific study. Diabetes affects 16 million people in the United States alone and it is the fourth leading cause of death. Insulin, the hormone produced by pancreas, regulates the uptake and conversion of sugar into heat energy and muscle power. Diabetes is a metabolic disorder and insufficient insulin production leads to Type 1 diabetes or insulin-dependent diabetes mellitus (IDDM). Lipid metabolism is often deranged in diabetics resulting in weight gain and other complications.

More than half of U.S. adults are overweight (body mass index, BMI >25), [illegible] (BMI >30), and 11% of children and adolescents are overweight. Approximately 300,000 deaths are attributable to obesity annually. Sedentary life style is prevalent as only 24% of U.S. adults exercise the recommended five times per week for at least 30 minutes. Healthy weight maintenance involves a delicate balance between energy intake and energy expenditure.

Glucose is the principle nutrient for energy and daily energy balance between intake and expenditure is a determining factor in body weight stability. A sustained positive energy balance leads

to weight [illegible] accounts for weight loss. Obesity is [illegible] and more acute in developed countries [illegible] style and rich diets among both adults and [illegible] to deleterious consequences such as obesity, [illegible], insulin resistance, diabetes and other health risks (York D, [illegible]. How obesity develops, Endocrine, 13 (2), 143-154, [illegible]. [illegible] is a metabolic disorder characterized by insulin [illegible] central obesity, high cholesterol, high blood pressure, high [illegible] sugar levels. An estimated 20 to 30% of middle-[illegible] [illegible] suffer from Syndrome X, which is believed to increase [illegible] and heart disease. The spread of obesity [illegible] epidemic in the U.S. and a sensible, sustainable [illegible] [illegible] in this environment (Mokdad AH, [illegible], [illegible] BA, Marks JS, Koplan JP. The spread [illegible], pleasure in the United States, 1991-1998, JAMA, 282 ([illegible], [illegible], [illegible]).

Glucose [illegible] important nutrient for many cells of the body. Glucose transport from the blood into cells, therefore, is one of the most [illegible] functions of all cells and some tissues, such as brain, are [illegible] dependent on glucose as an energy source. Insulin regulates glucose uptake into fat and muscle cells through the recruitment [illegible] transporter (GLUT)4 from an intracellular [illegible] pool to the plasma membrane. A complex [illegible] system keeps the blood glucose level constant in [illegible] cells contain several types of sodium linked glucose [illegible] known as GLUT family. Glucose transporters, [illegible], are especially important for regulation [illegible] and skeletal muscle cells and in fat [illegible]. The pancreatic hormone [illegible] by a cascade of biochemical [illegible], including activation and translocation of GLUT4 to cell surface, [illegible] transport from blood to cells (Yamasaki K, [illegible] Signaling on glucose transport system, Eds. Walker [illegible], [illegible]. Plenum Press, New York; Maier VH and Gould GW. [illegible] treatment of 3T3-L1 adipocytes results in [illegible] GLUT4: implications for

insulin-[illegible] transport, Diabetologia, 43, 1273-1281, 2000; [illegible] Klip A. Engagement [illegible] pathway in the stimulation of glucose [illegible] acid in 3T3-L1 adipocytes, Diabetologia, [illegible], 2000).

[illegible] systematically searching for an agent [illegible] activity and to find a natural product useful as an anti-diabetic agent. Various medicinal plants from Asia [illegible] treat diabetes and the plants exhibiting [illegible] include *Momordica Charantia*, *Tinospora* [illegible], etc. (Yamasaki K 1996). Tea preparations [illegible] *Speciosa L.*, traditionally [illegible] for weight-loss and by diabetics to balance [illegible] (Murakami [illegible], Ryoji K, Ohtani K, Kurokawa [illegible] and Yamasaki, K. Screening [illegible] for effect on glucose transport activity [illegible], Chemical and Pharmaceutical [illegible] (12), [illegible], 1993) and in-vitro studies [illegible] acid extracted from the leaves of *Lagerstroemia* [illegible] improves the cellular uptake of glucose (Murakami [illegible]). Further studies in diabetic mice indicate [illegible] of leaf-extracts from *Lagerstroemia* [illegible] (Kakuda T, Sakane I, Takihara T, Ozaki Y, Takeuchi H [illegible] K. Hypoglycemic effect of extracts from *Lagerstroemia* [illegible] leaves in genetically diabetic KK-AY mice, [illegible] (2), [illegible], 1996).

SUMMARY [illegible]

[illegible] and non-toxic Corosolic [illegible] gel formulation for increased [illegible] the human body. A preferred [illegible] includes Corosolic acid, rice bran oil, and [illegible]. The preferred soft gel Corosolic [illegible] administered thrice a day in dosages of about [illegible].

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graphical comparison of the sugar levels in volunteers taking nothing, Corosolic acid in gel form and Corosolic acid in powder form;

Figure 2 is a graph showing the washout rates of blood sugar level vs. time during and after taking gel and powder Corosolic acid;

Figure 3 is a comparison graph showing the blood sugar level vs. time during and after taking gel and powder Corosolic acid;

Figure 4 is a graph showing the washout rates of weight vs. time during and after taking gel and powder Corosolic acid;

Figure 5 is a graphical comparison of the weight of volunteers taking nothing, Corosolic acid in gel form and Corosolic acid in powder form; and

Figure 6 is a graph of weight change vs. dosage of Corosolic acid.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Corosolic acid (2α-hydroxyursolic acid, CAS# 52213-27-1; Glucosol™ (trademark of Bel Texrn Healths, Inc. of Los Angeles, CA) is a triterpene having a molecular weight of 743.63 grams and is a lipophilic, pentacyclic compound that is extracted from the leaves of *Lagerstroemia Speciosa L.* *Lagerstroemia Speciosa L.* is commonly known as Crape Myrtle and belongs to the botanical family *lythraceae*. It is a very common ornamental deciduous tree that grows in the tropics. Areas of the globe. Tea preparations from the leaves of *Lagerstroemia Speciosa L.*, traditionally have been used for [illegible] diabetics to balance blood sugar levels (Murakami et. al., [illegible].

Both in-vitro and in-vivo studies on the glucose transporter stimulatory activity of the extract from *Lagerstroemia Speciosa L.*, have been performed recently, including the identification of Corosolic acid (2α-hydroxyursolic acid, CAS# 52213-27-1), a triterpenoid, as the active principle of this extract and its hypoglycemic [illegible] (Matsuda et. al., [illegible]; Yamasaki, 1996; De Tommasi N, [illegible], Piacente S, [illegible], Pizza C,

Hypoglyc[illegible] polyhydr[illegible] Meica, 5[illegible]; [illegible], F. [illegible] Decoction [illegible] Orally. [illegible] *Philippine Medical Association*, 22, #7, 395402, [illegible]; [illegible], A. [illegible] Insulin-[illegible] *Medica Philippina*, [illegible]; [illegible], F., and Melencio-Maglalang, P. Applicati[illegible] Diabetics. *The [illegible] Philippine Medical Association*, 33, #1, 7-16, [illegible]; [illegible], F. [illegible] Articles [illegible] *the Philippine* [illegible], [illegible], #5, [illegible], 1959; Garcia, L., [illegible], [illegible], [illegible], F. and Capal, T. Pharmacol[illegible] from Lagerst[illegible]. *The Philippine Journal of Science*, 116, #4, [illegible]; [illegible] et al., Int. J. Tiss. Reac., 1983, X(2), [illegible]). Furthermore, according to the descriptions in the following [illegible], extracts from these plants administered to rats at [illegible] significant reduction in blood sugar levels. [illegible], studies in rats based on a single oral limit-dose [illegible] that [illegible] acid is safe and non-toxic.

The [illegible] was conducted using the soft-gelatin [illegible] Acid (Glucosol™) to evaluate [illegible] effects in Type 2 diabetics. [illegible] was conducted in normal subjects to compile [illegible] acid.

Blood [illegible]:

A [illegible] type 2 diabetes (six men of [illegible] pounds [illegible] 74 years of age with a weight range of [illegible]) were given an oral daily dose of 48 mg Glucosol™ [illegible] days followed by a 45 day wash-[illegible]. [illegible] given over to an oral

daily dose [illegible] Glucosol™ in a hard gel capsule formulation for 30 days [illegible] wash-out period. Each volunteer provided a [illegible] in the morning, after an over night fast, seven days [illegible] of the study (-7 day) and on the day of the study (1 day) [illegible] fasting blood glucose levels. Subsequently, [illegible] level and body weight were measured at 15-day intervals [illegible] duration of the study.

Blood glucose [illegible] and weight-loss:

In this [illegible] study, at a daily dose of 48 mg of Glucosol™, both soft [illegible] and hard gel formulations show a statistically significant ($p < 0.05$) reduction in blood glucose levels compared [illegible] fasting measurements (Figures 1, 2, and 3). [illegible] fasting levels, the relative reduction in blood glucose [illegible] was similar to that observed in the dose-response study; 21.6% decrease in the soft gel and 22.6% decrease in the hard gel formulation. However, compared to the dry-powder [illegible] preparation, the soft gel form of Glucosol™ shows a significantly ($p < 0.05$) greater ability to lower blood glucose levels. Further, the slow recovery of blood glucose levels during the wash-out [illegible] for both formulations suggests an after-effect [illegible] of Glucosol™, even after the cessation [illegible] daily dose of Glucosol™ which suggests a significant [illegible] daily-dose compliance issue for diabetics.

Concomitant with the reduction in fasting glucose levels, a weight-loss [illegible] was observed [illegible] of Glucosol™ (Figures 5 and 6). However, the weight-loss during the wash-out period was significantly [illegible] the after-effect or memory-effect of Glucosol™. No [illegible] was also observed during the dose-response study. The differences in weightloss between the soft gel and hard gel formulations are significant at 32 and 48 mg/day Glucosol™ [illegible].

Acute and [illegible] oral [illegible] of Tartaric acid (Glucosol™) [illegible] in healthy [illegible] at daily dose of 48 mg Glucosol™ [illegible] fasting blood glucose remain in the

normal [illegible] and after the intake of Glucosol™. [illegible] and hematology profiles did not [illegible] indicating the safety profile of Glucosol™. [illegible] weight-loss observed [illegible] Glucosol™ at 48 mg per day for [illegible]. [illegible] was 1.25 ± 0.6 pounds after [illegible] day use of Glucosol™.

Therefore, [illegible] of leaf extract of *Lagerstroemia speciosa L.* standardized to 1% Corosolic acid (Glucosol™) exert a marked [illegible] in type 2 diabetics and also a significant [illegible] weight-loss without any adverse effects. Further, [illegible] that Glucosol™ does not alter either [illegible] of blood sugar in non-diabetic [illegible], which is responsible for the weight-loss effect.

Similarly, [illegible] demonstrated a significant [illegible] weight-loss effect comparable to Glucosol™ formulated in a dry-powder hard gelatin capsule, [illegible] the triterpene active ingredient in Glucosol™ is [illegible] when administered in an oil-based soft gelatin capsule formulation.

Although [illegible] a significant dose-response relationship [illegible] up to 48 mg per day, the top of the dose-response curve [illegible] has been achieved so the maximum dose to achieve a [illegible] response is unknown.

It is an [illegible] of the present invention to provide an improved [illegible] acid, including a soft gel formulation [illegible] and sustained weight-loss and an [illegible]. In this regard, this formulation contains [illegible] of *Lagerstroemia L.* standardized to 1% Corosolic acid (Glucosol™) [illegible].

It is [illegible] of the present invention to provide a soft [illegible] administration that produces [illegible].

The [illegible] the following sequence of ingredients:

1. [illegible]

2. Addition [illegible] silica.

3. Simultaneously [illegible] the following ingredient: Glucosol™ ([illegible] acid but an aqueous [illegible]).

4. Blending [illegible] ingredients.

5. Cooling [illegible] (about 22 °C).

6. Thereafter [illegible] of the container.

7. Soft gel [illegible].

In summary, [illegible] in-vitro, pre-clinical (animal) and clinical studies [illegible] *Lagerstroemia speciosa* L., [illegible] beneficial effects of blood-sugar lowering and anecdotal [illegible] effects. Recent clinical studies establish the [illegible] of *Lagerstroemia speciosa* L. standardized [illegible] acid (Glucosol™) formulated into a soft gel [illegible]. Additional studies with this new formulation [illegible] suggest improved bioavailability and absorption [illegible] in an oil-based soft gel capsule formulation [illegible] a hydrophilic gel gelatin capsule formulation.

In addition, [illegible] may also incorporate an extract of [illegible], known for its benefit for weight loss through [illegible], as an additional ingredient. The present [illegible] soft gel formulation, with the addition of [illegible] vitamins A and E, B complex vitamins, as well as [illegible] Alpha Lipoic Acid, DHA, and the mineral chromium, [illegible] in a balanced weight loss program.

Thus [illegible] novel formulations, methods, and [illegible] objects and advantages sought therein. Many [illegible] variations and applications [illegible] will become apparent to those skilled in the art [illegible] specification and the accompanying [illegible] manner, modifications, alterations and other [illegible] without departing from the spirit and scope [illegible] covered by the invention [illegible] claims that follow: